Consequences of local recurrence of soft tissue sarcoma

205 patients from the Scandinavian Sarcoma Group Register

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ABSTRACT – From the Scandinavian Sarcoma Group Register, information on 1,224 surgically-treated patients with soft tissue sarcoma (STS) of the extremity or trunk wall, diagnosed between 1987 and 1995, was collected. 205 patients, one third of whom were referred to a center with a local recurrence, had a total of 284 local recurrences. This analysis describes the treatment for these local recurrences, complications and risk of further recurrences.

169 patients were surgically treated for their first local recurrence. An intralesional or marginal margin was achieved in 110 of these patients, 59 of whom were also given radiotherapy. 54 of the 169 patients had a second local recurrence. The second local recurrence rate was 0.50 if the first local recurrence had been treated with only surgery with a marginal margin, compared to 0.28 if treated with surgery with a marginal margin and radiotherapy or with a wide margin (p = 0.0008). In extremity STS, the crude amputation rate for local recurrences was 0.22 (31 of 142)—i.e., higher than for primary tumors 0.09 (96 of 1065) (p < 0.0001).

A high local recurrence rate after treatment outside of sarcoma centers has earlier been shown. We conclude that the consequences of local recurrence in terms of morbidity and costs justifies referral of STS patients for multidisciplinary evaluation and multimodality treatment.

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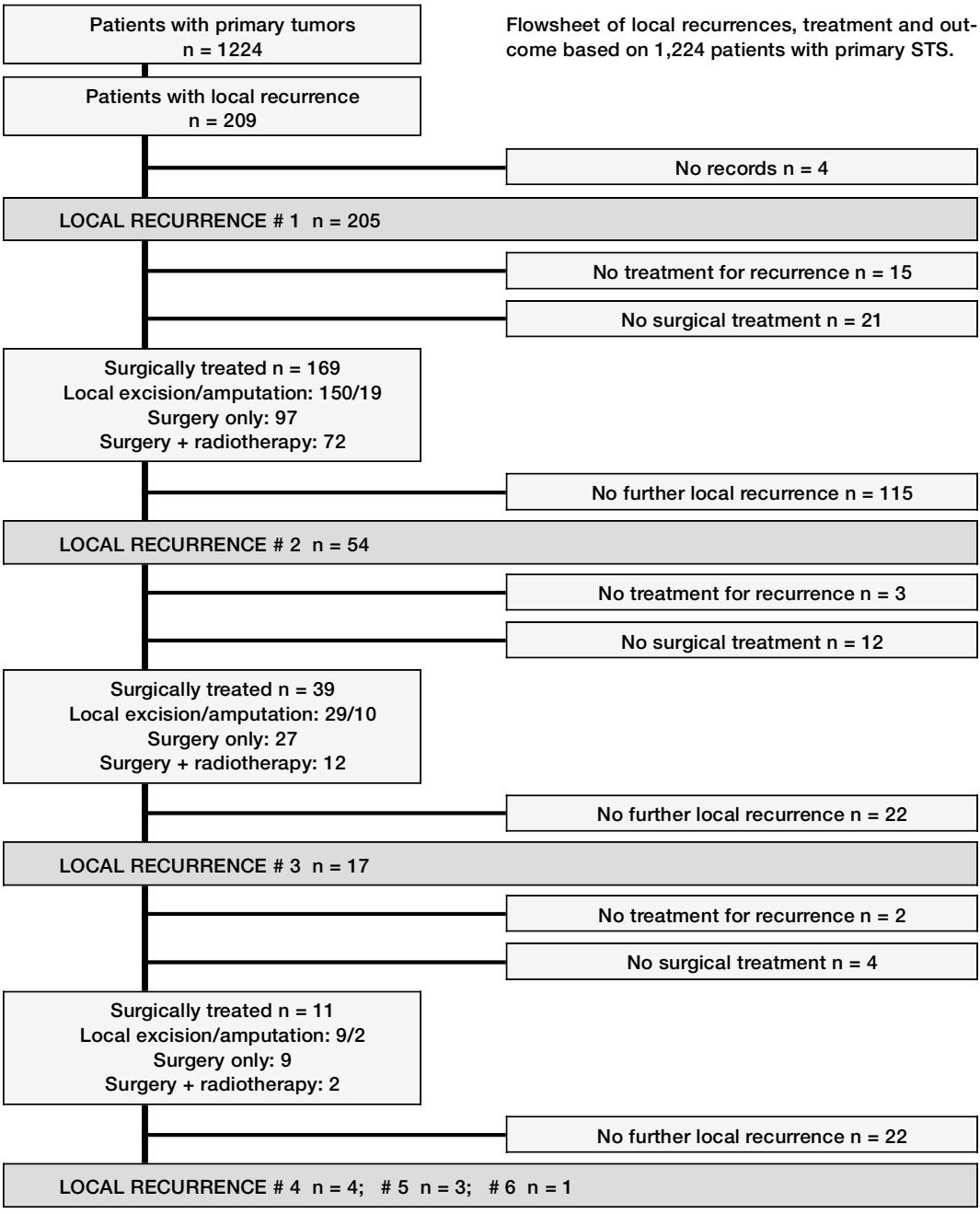
Amputation for extremity-localized STS is uncommon, but little is known about the amputation rate after local recurrence (Gustafson 1994, Williard et al. 1992a,b, Coindre et al. 1996). 15 years ago, amputation was recommended for local recurrence because limb-sparing surgery was thought to carry an unacceptably high risk of a second local recurrence (Guiliano et al. 1982). The possibility of limb-sparing surgery is reduced by the problems of achieving an adequate surgical margin and by the increased risk of complications after previous surgery and radiation therapy (Arbeit et al. 1987, Chmell and Schwartz 1996).

The aim of the present study was to assess treatment for local recurrence, based on 205 patients with a total of 284 local recurrences, reported to the Scandinavian Sarcoma Group (SSG) Register.

Patients and methods

The SSG Register has collected information on adult STS patients in Scandinavia since 1986 (Bauer et al. 1999). Clinical, histopathologic, and follow-up data were recorded. Between January 1987 and November 1995, 1,224 patients with STS of the extremity and trunk wall were surgically treated at 9 Swedish and Norwegian sarcoma centers (Appendix). 209 of these 1,224 patients had a local recurrence, and 63 of these, by the time



Flowsheet of local recurrences, treatment and outcome based on 1,224 patients with primary STS.

of referral to a tumor center. Complete information was available for 205 patients who had altogether 284 local recurrences (Figure, Table 1).

All patients (n 1,224)

Of the 1,224 patients, 652 were men. 733 patients were referred with untouched tumors or after needle aspiration cytology, 392 after surgical intervention for the primary tumor, 63 after a local recurrence, while the remaining 36 patients were not referred, but identified by national cancer registries. The thigh was the commonest site (n 407), followed by the lower leg (n 144). The median tumor size was 7 (1–55) cm. 388 tumors were sub-

Table 1. Distribution of histotypes in relation to number of local recurrences in 205 patients with locally recurrent soft tissue sarcoma of extremity and trunk wall. Total number of local recurrences = 284

Histotype	Local recurrence					
	1st	2nd	3rd	4th	5th–6th	Total
MFH [a]	98	31	14	4	4	151
Fibrosarcoma	20	4	1	0	0	25
Leiomyosarcoma	19	6	1	0	0	26
Liposarcoma	17	1	0	0	0	18
MPNST [b]	12	2	1	0	0	15
Epithelioid cell sarcoma	8	2	0	0	0	10
Synovial sarcoma	6	0	0	0	0	6
Unclassified sarcoma	10	3	0	0	0	13
Other sarcomas	15	5	0	0	0	20
Total	205	54	17	4	4	284

[a] MFH malignant fibrous histiocytoma
[b] MPNST malignant peripheral nerve sheath tumor.

cutaneous and 836 deep-seated, i.e., located in or deep to the fascia, either intra- or extramuscular.

Patients with local recurrence (n 205)

Of the 205 patients with local recurrence, 106 were men. The median age at diagnosis of the primary tumor was 67 (20–91) years. The thigh was the commonest site (n 54), followed by the trunk wall (n 32). The median primary tumor size was 7 (1–32) cm. 65 of the primary tumors were subcutaneous, and 140 were deep-seated. Malignant fibrous histiocytoma (MFH) was the commonest histotype (n 98). 35 of the primary tumors had been removed with an intralesional margin (in 10 patients, adjuvant radiotherapy was given), 95 with a marginal margin (21 with adjuvant radiotherapy), 65 with a wide margin (5 with adjuvant radiotherapy), and 10 with a compartmental margin.

Diagnostic procedures, treatment and complications were recorded for each local recurrence. Surgical margins were classified according to Enneking et al. (1980). Histopathological evaluation and malignancy grading (four-grade scale) were according to Angervall and Kindblom (1993). Amputation rates, surgical margins, operation times and reconstruction procedures were recorded for all surgical events.

Based on the work by Arbeit et al. (1987), surgical complications were categorized as major, moderate or minor. A major complication was when a second operation was necessary for wound coverage, or when the limb was threatened. Moderate complication included persistent seroma requiring more than three aspirations, hematoma > 25 mL, wound separation > 2 cm, or purulent wound discharge. Minor complications were seroma < 75 mL resolving after less than three aspirations, hematoma < 25 mL, or wound separation < 2 cm. Wound erythema, or use of antibiotics without clinical evidence of infection were not considered as complications.

The 205 patients were followed through June 1997, for a minimum of 14 months after their last local recurrence, or until death. All 169 patients who were surgically treated for their first local recurrence were followed for a minimum of 20 months, until death or a second local recurrence. The median follow-up of those free of a second local recurrence was 48 (15–120) months. Of 124 patients who had died at the last follow-up, 91 had died of tumor-related causes at a median of 18 (1–107) months after diagnosis of their first local recurrence. Treatment with chemotherapy and/or radiotherapy was recorded and correlated with surgical margins and rate of metastasis. The risk of having a second local recurrence, relative to adjuvant radiation treatment, was assessed by Kaplan-Meier technique.

Table 2. Local and systemic treatment for first local recurrences in 205 patients with locally recurrent soft tissue sarcoma of extremity and trunk wall. Patients with metastasis at the time of diagnosis of the first local recurrence in parentheses

	No surgery	Intralesional	Marginal	Wide	Radical	Total
Radiotherapy	9 (3)	6	49 (5)	12 (2)	1	77 (10)
Chemotherapy	8 (4)	6 (4)	5 (4)	4 (1)	1 (1)	24 (14)
Radio- + chemotherapy	4 (3)	0	4 (2)	0	0	8 (5)
None	15 (5)	7 (1)	33 (2)	40 (2)	1	96 (10)
Total	36 (15)	19 (5)	91 (13)	56 (5)	3 (1)	205 (39)

Results

First local recurrence (n 205)

The median time to the first local recurrence was 12 (2–94) months. 158 (77%) were diagnosed within 2 years, 182 (89%) within 3 years, and 201 (98%) within 5 years. Following clinical examination, the diagnosis of local recurrence was made by needle biopsy in 108 patients, by open biopsy in 12, and by radiological examination in 27. Routine radiological investigation of the tumor bed was not part of the follow-up examination, but CT or MRI was performed in patients if the tumor bed could not be easily palpated. In 58 patients, the palpable recurrence was removed without prior diagnostic procedures. At the time of diagnosis of the first local recurrence, 39 of the 205 patients also had metastases (Table 2).

169 of the 205 patients with a first recurrence were surgically treated. An intralesional or marginal margin was achieved in 110 patients, of whom 59 were also given adjuvant radiotherapy. 6/19 patients with an intralesional margin received radiotherapy. A wide or compartmental margin was achieved in 59 patients. Adjuvant chemotherapy was part of the total treatment for the local recurrence in 32 of the 205 patients (Table 2). 19 of these 32 patients had metastases at the time of local recurrence and were given chemotherapy for this reason. Another 10 were given palliative chemotherapy because the local recurrence was unresectable or was only debulked, and 3 had adjuvant chemotherapy after excision of the local recurrence with a wide or compartmental margin to reduce the risk of later metastatic disease.

Table 3. Local and systemic treatment for 79 second and subsequent local recurrences in 54 patients with locally recurrent soft tissue sarcoma of extremity and trunk wall. Patients with metastasis at the time of diagnosis of the local recurrence in parentheses

	No surgery	Marginal	Wide	Total
Radiotherapy	6 (2)	14	1	21 (2)
Chemotherapy	6 (2)	3 (1)	0	9 (3)
None	12 (4)	24 (3)	13 (1)	49 (8)
Total	24 (8)	41 (4)	14 (1)	79 (13)

Second and subsequent local recurrences (n 79)

Of the 169 patients surgically treated for their first local recurrence, 54 had a second local recurrence after a median of 10 (1–70) months. Among 19 patients with intralesional margins, 3 patients had a second local recurrence, 12 had died before developing a second recurrence. The overall 3-year risk of having a second local recurrence was 0.33. Among 118 first local recurrences treated with a marginal margin with adjuvant radiotherapy or with a wide margin, the risk was 0.28, compared to 0.50 in 51 first local recurrences treated with surgery alone with a marginal margin ($p = 0.0008$).

Of the 39 patients who underwent surgery for their second local recurrence, 17 had a third local recurrence after a median 12 (2–36) months. 4 patients had 4 local recurrences, 3 had 5, and 1 had 6 local recurrences (Figure, Table 1). 55 of the 79 second and subsequent local recurrences were surgically treated. A marginal margin was achieved in 41 patients, of whom 14 were also given adjuvant radiotherapy, and a wide or compartmental margin was achieved in 14 patients (Table 3).

Table 4. Reconstruction procedures for wound closure in 190 patients operated on for locally recurrent soft tissue sarcoma

Type of reconstruction	n
None	135
Split-skin graft	21
Pedicle graft/free flap	21
Vascular reconstruction	6
Artificial trunk wall/pedicle or free flap or allograft	7

Table 5. Wound complications in relation to radiotherapy in 147 of 169 patients surgically treated for a first local recurrence of soft tissue sarcoma. Radiotherapy was given after surgery for the primary tumor or the local recurrence. Severity of complication classified according to Arbeit et al. (1987)

Severity of complication	No previous radiotherapy	Radiotherapy
Major	6	7
Moderate	8	17
Minor	7	9
None	46	47
Total	67	80

All local recurrences

65 of the 205 first local recurrences originated from subcutaneously-located primary tumors, while 23 of the 54 second, and 8 of the 17 third local recurrences originated from such tumors. The commonest site was the thigh (74 of 284), but the relative proportion located in the upper extremities increased with the number of recurrences; 43 of 205 of first local recurrences, compared to 6 of 17 of third local recurrences. The proportion of MFH increased with an increasing number of local recurrences, i.e., only MFH recurred more than three times (Table 1).

The crude amputation rate for the 1065 patients with extremity localized primary STS was 0.09 (96 of 1065), compared to 0.22 (31 of 142) for patients with extremity local recurrences ($p < 0.0001$). 19 patients were amputated for their first local recurrence, and an additional 12 patients for a second or subsequent local recurrences.

Information on reconstructive procedures for soft tissue closure could be retrieved in 190 of 205 patients. In 55 patients, such procedures, including split-skin grafts, were used (Table 4). Patients who had more than one local recurrence tended to have fewer reconstructive procedures done—i.e., 49 of 147 patients with only one local recurrence had a reconstructive procedure done, compared to 10 of 43 with 2 or more local recurrences ($p = 0.08$).

Wound complications could be evaluated in 199 of the 224 operations performed for local recurrence. The wound healed uneventfully in two thirds of the operations. Major complications occurred after 20, moderate complications after 32, and minor complications after 20 operations. There was no association between previous radiotherapy and wound complications, and the risk of such complications was not dependent on whether radiotherapy was given for a primary tumor or a local recurrence (Table 5). Seven patients were given adjuvant radiotherapy for both a primary tumor and local recurrence; of these, 2 had moderate wound complications.

Discussion

It is well known that patients with local recurrences more often develop metastasis. This has been interpreted as the local recurrence which is the source of the metastasis (Markhede et al. 1982, Emrich et al. 1989, Stotter et al. 1990, Trovik and Bauer 1994). However, this view has been questioned, and today local recurrence is regarded as a sign of poor quality of the local treatment, but also of a more malignant tumor, with potential for metastatic spread (Gustafson 1994, Trovik et al. 2000). Hence, a reduction in local recurrence rates may not directly lead to improved survival (Yang and Rosenberg 1989, Tanabe et al. 1994, Pisters et al. 1996, Lewis et al. 1997). Furthermore, patients with a local recurrence but without concurrent metastasis as a group have a prognosis as good as those who never develop a local recurrence (Gustafson et al. 1993). This non-causal interpretation of the association between local recurrence and metastasis implies different treatment approaches for the primary tumor. Today, no consensus exists as regards acceptable local recurrence rates and rates of amputation. The use of adjuvant therapy consequently varies among different re-

gions of the world. Most STS patients would receive radiotherapy in USA, while in Scandinavia only 25% received such treatment (Bauer et al. 1999).

Modern centralized and multimodality treatment of STS has reduced local recurrence rates to less than 15% (Sadoski et al. 1993, Wiklund et al. 1993, Yang et al. 1998). In contrast, local recurrence rates in excess of 40% can be expected when STS are treated at local hospitals (Gustafson et al. 1994, Clasby et al. 1997).

This series was not population-based. However, we believe that the results are applicable to treatment of STS in general, since there is no reason to assume that we have identified a subset of local recurrences "more complicated or expensive to treat" than usual. Furthermore, the patients having a local recurrence were identified in a base series, with patient characteristics similar to population-based series (Gustafson 1994).

As has been reported (Robinson et al. 1990), local control was more difficult to achieve after local recurrence than after primary tumors. For local recurrences, the possibility of achieving wide margins without resorting to amputation may be limited, partly due to distorted anatomy after previous treatment. Previous radiotherapy may also preclude further use of this modality. In this series, a reduction in second and subsequent local recurrence rates would be expected if more patients had been given radiotherapy for the first recurrence. Altogether, only half of the patients had had radiotherapy for the primary tumor or the local recurrence. While most superficial and small STS may be managed without radiotherapy, there is a definite indication for radiotherapy for a local recurrence, probably regardless of margin or grade.

The rate of wound complications reportedly increases after radiation treatment (Robinson et al. 1990, Brennan et al. 1991). Limb-sparing surgery for local recurrence has been associated with a higher complication rate than for a primary tumor (Stotter et al. 1988). In this series, there were also more, but not significantly, moderate and severe surgical complications associated with radiotherapy. Furthermore, the complication rates were comparable to those after primary surgery (Arbeit et al. 1987, Skibber et al. 1987, Bell et al. 1989, Chang et al. 1989, Paz et al. 1992, Saddegh and Bauer 1993, Peat et al. 1994, Chmell and Schwartz 1996). It is difficult to compare complication rates as there is no universally accepted method for categorizing wound complications. We used the method of Arbeit et al. (1987) which was developed at the Sloan-Kettering Memorial Hospital for surgery and brachytherapy of STS. In conclusion, however, the use of radiotherapy in local recurrence treatment does not seem to increase the number of complications significantly.

A more frequent use of radiotherapy for the primary lesion would increase the cost of treatment. Only 10% of patients required hospitalization during radiotherapy so this adjuvant treatment adds little to the total costs.

Cellular mechanisms involved in metastasis or local recurrence are only partly becoming clear. One subset of tumors has a capacity both for local and metastatic growth; these patients often have early and simultaneous local and distant failure. Another subset of patients seems to have a tendency towards local failure, but not metastasis. In this series, these tumors were more often small MFH of subcutaneous origin. They were mostly situated in the upper extremity, which is probably due to the greater difficulties of achieving a wide margin, compared to the trunk or lower extremity, and the reluctance to resort to amputation.

We conclude that local recurrences are expensive and complicated to treat. Both amputation rates and local recurrence rates were twice as high as those for treatment of primary tumor. Generous referral of patients with soft tissue lesions to sarcoma centers before biopsy or surgery is cost-effective; the higher local recurrence rates in patients treated for STS outside tumor centers outweighs the costs for the necessary over-referral of patients whose lesions turn out to be benign.

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Appendix

Participating sarcoma centers. In Sweden: Karolinska Hospital, Stockholm; University Hospital,

Lund; Sahlgrenska University Hospital, Gothenburg; University Hospital, Umeå; University Hospital, Linköping, and in Norway: The Norwegian Radium Hospital, Oslo; Haukeland University Hospital, Bergen; University Hospital, Trondheim; and Ullevål Hospital, Oslo.

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